

## REMARKS

### In the claims

Claims 15, 18, and 32-46 are canceled without prejudice or disclaimer.

Amended claim 14 is directed to the method of claim 11, wherein the pain is caused by or associated with damaged sensory neurons. Support is provided, *e.g.*, in the treatment of hyperalgesia caused by or associated with damaged sensory neurons in Example 2.

Amended claim 17 is directed to the method of claim 11, wherein the pain is caused by or associated with inflammation. Support is provided, *e.g.*, in Example 1, which uses carrageenan as an inflammatory stimulus in the rat.

Claim 27 is amended in view of the Examiner's request to clarify language. Claim 28 is amended to maintain antecedent basis. These amendments are not intended to limit claims 27 or 28 in any way.

New claim 47 recites "wherein the spongiosine is administered to the subject when the subject is at risk of developing inflammation." New claim 48 recites "wherein the spongiosine is administered to the subject when the subject is contacted with an inflammatory stimulus." Support is provided, *e.g.*, in Example 1, as noted above. In particular, as an inflammatory stimulus, "[c]arrageenan (2%, 10 microlitres) was administered into the right hind paw," and "[s]pongiosine was administered at the same time as carrageenan."

New claim 49 recites "wherein the spongiosine is administered to the subject when the subject is at risk of developing pain." New claim 50 recites "wherein the spongiosine is administered to the subject before the subject is exposed to a pain stimulus." New claim 51 recites "wherein the pain is associated with or caused by inflammation." New claim 52 recites "wherein the pain is associated with or caused by thermal hyperalgesia." Support is provided, *e.g.*, in Example 1 as above, and further because the carrageenan and the spongiosine are administered before "[a] heat source was placed close to the treated and untreated hind paws" as a pain stimulus" (before because the heat source was placed close to the treated paw).

No new matter is added by the preceding amendments. The Examiner is respectfully requested to enter and examine the amended claims.

### **Purpose of Claim Cancellations and Amendments**

Applicant respectfully notes that the claim cancellations and amendments (*e.g.*, canceled claims 15, 18, and 32-46, and amended claims 14, 17, 27 and 28) are made solely in order to clarify the claims for appeal, in the event Applicant elects to appeal any rejection which might be applied or maintained against the pending claims. By making these cancellations and amendments, Applicant does not acquiesce to or acknowledge the propriety of any rejection or objection, nor does Applicant intend to narrow the scope of independent claim 11 in any way. Further, Applicant does not intend to relinquish rights to any subject matter removed by such cancellations and amendments, but rather reserves the right to file a continuation application or to take any other action to preserve rights to such subject matter.

### **Obviousness Rejections under 35 U.S.C. § 103(a)**

Claims 11-46 stand rejected under 35 U.S.C. § 103(a) as being obvious over Fukunaga, U.S. Pat. No. 5,677,290 ("Fukunaga '290") in view of Fukunaga, *et al.* U.S. Pat. No. 5,679,650 ("Fukunaga *et al.* '650," or collectively "the Fukunaga patents") and further in view of Ueeda *et al.*, Life Sciences, 49(18), 1351-1358 (1991) (Ueeda *et al.*).

Since claims 15, 18, and 32-46 are canceled, the rejection thereover is moot and should be withdrawn.

### **Summary of Examiner's Argument**

The Examiner alleges that Fukunaga '290 discloses that adenosine or analogues thereof can cause relief from pain and inhibition of inflammatory "stress" while avoiding hypotension, whereas Fukunaga *et al.* '650 discloses that adenosine or adenosine analogues administered with catecholamine modulates side effects associated with fentanyl and can minimize damage from disease conditions including ischemia. The Examiner alleges that antihypertensive, antinociceptive, and anti-inflammatory effects of adenosine are notoriously well known. The Examiner concedes that the Fukunaga patents do not expressly disclose 2-methoxyadenosine as an active ingredient in any method of treatment. The Examiner alleges that Ueeda *et al.* discloses that "2-ethoxyadenosine has binding constants at adenosine receptors that vary very

little from the binding constants for adenosine, for R-PIA and for NECA,” concluding that “substitution of an adenosine analog ... [is] expected to produce a similar ... analgesic effect.”

The Examiner concludes that it would have been obvious to “substitute compounds very closely analogous” to the Ueeda *et al.* compounds into the Fukunaga methods because “the Fukunaga references explicitly teach the pharmacological equivalence of adenosine and adenosine analogues.” The Examiner alleges that the motivation to combine exists because they are “directed to overlapping disclosures of the medicinal administration of adenosine and analogues of adenosine ... to treat various disease conditions including pain...”

The Examiner alleges that “The Homology Rule” states that a methylene homologue of a known compound is *prima facie* unpatentable absent unexpected results; that 2-ethoxyadenosine of Ueeda *et al.* and 2-methoxyadenosine (spongiosine) are homologous; and thus the claims are rendered obvious. The Examiner alleges that Applicant's did not overcome the Examiner's assertion that the Ueeda *et al.* compounds “including adenosine, have binding constants (where measurement was possible) that vary very little.” The Examiner maintains the rejection absent a sworn showing that the analgesic effect of spongiosine is measurably, and unexpectedly, different from that of adenosine.

### ***Summary of Applicant's Argument***

Applicants respectfully disagree with the Examiner's analysis and submit that the claimed methods are patentable over Fukunaga '290 in view of Fukunaga *et al.* '650, and further in view of Ueeda *et al.* for any of several reasons, as discussed in detail below.

First, as the Examiner's rejection appears to use homology as a *per se* rule of obviousness, Applicant emphasizes that there are no *per se* rules of obviousness. A determination of whether invention exists over the prior art under 35 U.S.C. § 103(a) is to be decided on specific facts. For example, structural homology is a fact which may be considered in a determination of obviousness but is not a *per se* rule of obviousness.

Second, structural homology cannot support obviousness without a valid expectation that homologous compounds will have similar properties. Such an expectation is contradicted by the Ueeda *et al.* reference. As detailed in Applicant's previous response (filed November 19, 2007) and explained again below, the compounds cited by the Examiner are shown in Ueeda *et al.* to

have **substantially different binding constants** compared with 2-ethoxyadenosine at A<sub>1</sub>A and A<sub>2</sub>A receptors<sup>1</sup>. Moreover, Ueeda *et al.* and other art would lead one of skill to expect that weak A<sub>2</sub>A receptor agonists such as 2-ethoxyadenosine and spongine (2-methoxyadenosine) would **cause** peripheral pain, as well as side effects of hypotension and tachycardia. One of skill would be led instead to A<sub>1</sub>A receptor agonists to treat pain, particularly selective, high affinity A<sub>1</sub>A receptor agonists.

Third, because the compounds cited by the Examiner from the Fukunaga patents have substantially different binding constants compared to 2-ethoxyadenosine, Ueeda *et al.* provides no reason or motivation to use 2-ethoxyadenosine in the methods of the Fukunaga patents. A showing of motivation cannot be based on broad conclusory statements lacking evidentiary support. Because the Examiner's argument presents **no evidence, and does not address Applicant's evidence**, it cannot support a reason or motivation to combine Ueeda *et al.* with the Fukunaga patents to arrive at the claimed method.

Fourth, because Ueeda *et al.* provides no motivation to use 2-ethoxyadenosine in the methods of the Fukunaga patents, the Examiner's homology analysis between 2-ethoxyadenosine and spongine (2-methoxyadenosine) is not relevant. The focus of homology analysis, if to support the Examiner's argument at all, would be to show that compounds cited by the Examiner are structurally homologous to 2-ethoxyadenosine (which they are not), and further, that these allegedly homologous compounds share similar binding constants (which they do not).

Consequently, for at least these reasons, a *prima facie* case of obviousness has not been made and the claimed methods are patentable over Fukunaga '290 in view of Fukunaga *et al.* '650, and further in view of Ueeda *et al.*

#### ***There are no per se rules of obviousness***

Before addressing of the specific points raised by the Examiner in the Final Office Action, Applicant wishes to clarify that there are no per se rules of obviousness of any kind. There is no legal precedent for *per se* rules of obviousness, it is improper to extract such rules from the case law, and it is legally incorrect to apply *per se* rules of obviousness.

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<sup>1</sup> The art uses varying receptor notation, e.g., A<sub>2</sub>, A<sub>2</sub>A, and A<sub>2</sub>AR; for consistency, this reply uses the A<sub>2</sub>A notation.

We once again hold today that our precedents do not establish any *per se* rules of obviousness, just as those precedents themselves expressly declined to create such rules. Any conflicts as may be perceived to exist derive from an impermissible effort to extract *per se* rules from decisions that disavow precisely such extraction *In re Ochiai* 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) (underline emphasis added; italics in original).

The obviousness inquiry under 35 U.S.C. § 103(a) is “highly fact-specific by design.” *Ochiai* at 1131. “Whether invention exists over prior art isomers and homologues is a question to be decided in each case.” *In re Henze* 85 USPQ 261, 264 (CCPA 1950). As the Federal Circuit explained in *Ochiai*:

...the examiner incorrectly drew from *Durden*, a case turning on specific facts, a general obviousness rule: namely, that a process claim is obvious if the prior art references disclose the same general process using similar starting materials.<sup>5</sup> No such *per se* rule exists. Mere citation of *Durden*, *Albertson*, or any other case as a basis for rejecting process claims that differ from the prior art by their use of different starting materials is improper, as it sidesteps the fact-intensive inquiry mandated by section 103. In other words, there are not ‘*Durden* obviousness rejections’ or ‘*Albertson* obviousness rejections,’ but rather only section 103 obviousness rejections. *Ochiai* at 1131 (italics in original).

Therefore, a proper obviousness inquiry under 35 U.S.C. § 103(a) is highly fact-specific, and a determination of whether invention exists over the prior art is a question to be decided on those specific facts. For example, structural homology, if present, is a fact which may be considered in a determination of obviousness and may lead to a presumption of obviousness, but is not itself a *per se* rule capable of rendering the claimed invention obvious.

***Structural similarity does not give rise to obviousness in the absence of similar properties***

Because compounds cited by the Examiner from the Fukunaga patents are shown in *Ueeda et al.* to have substantially different binding constants at A<sub>1</sub>A and A<sub>2</sub>A receptors as compared with 2-ethoxyadenosine, and other art at the time of the invention would lead one away from weak A<sub>2</sub>A receptor agonists such as 2-alkoxyadenosines, any structural homology asserted by the Examiner is insufficient to render the claimed method obvious.

“[I]t is not structural similarity alone that gives rise to obviousness, but the concomitant assumption that the structurally similar compounds will have like properties.” *Ex Parte Chwang* 231 USPQ 751, 752 (Bd. Pat. App. & Int’f 1986).

“Homology” implies that one or more similarities (e.g., in structure and/or properties) exist among a particular family compounds. However, there also exists **differences** as well as similarities among compounds grouped according to a structural classification system. As the Court of Customs and Patent Appeals (CCPA) explained in *In re Mills* 126 USPQ 513 (CCPA 1960) with regard to homology:

[H]omology provides for the chemist a convenient system of structural classification; inherent in that system are differences as well as similarities in properties and reactions of members of any given homologous series; *Mills* at 514.

#### Alkoxyadenosines Are Not Homologous to the Fukunaga Compounds

The Examiner concedes that there is no express disclosure of “2-methoxyadenosines as an active ingredient in any method of treatment” in Fukunaga ‘290 and Fukunaga *et al.* ‘650. Moreover, as noted in Applicant’s previous response (filed November 19, 2007), neither Fukunaga ‘290 nor Fukunaga *et al.* ‘650 teach or suggest alkoxy substituted adenosines much less 2-alkoxy substituted adenosines in any method of treatment. According to Fukunaga ‘290:

“[t]he term “adenosine compound” denotes compounds such as adenosine and adenine nucleotides, as well as derivatives and analogs of adenosine and ATP. As used herein, the “adenine nucleotides” are adenosine monophosphate, adenosine diphosphate, and adenosine triphosphate. In general, the preferred adenine nucleotide is adenosine triphosphate (ATP)” (Fukunaga ‘290, col. 3, ll 53-59).

According to Fukunaga *et al.* ‘650, the compounds include adenosine, phosphorylated adenosine, 5'-N-ethylcarboxamidoadenosine (NECA), R(-)N<sup>6</sup>-(2-phenylisopropyl) adenosine (R-PIA), 2-chloroadenosine, N<sup>6</sup>-cyclopentyladenosine, and N<sup>6</sup>-cyclohexyladenosine (claim 1 and col. 11, ll 26-32). Further, Applicant wishes to point out that the Fukunaga patents essentially only describe the specifically disclosed compounds. Terms such as “adenosine compound,” “derivatives and analogs of adenosine,” and the like are too vague and broad to provide any specific teaching or suggestion whatsoever of any particular group of compounds.

One of skill in the art would recognize that alkoxyadenosines have significantly different shapes, dipole moments, etc from the specific compounds described in the Fukunaga patents. Accordingly, a person of skill would not necessarily conclude that the Fukunaga compounds would have the same properties as spongosine (2-methoxyadenosine). In other words, a person of skill in the art may reasonably conclude that they would have different properties.

### 2-Ethoxyadenosine Differs Substantially from the Fukunaga Compounds in $K_i$ and Selectivity

The Examiner purports to address the deficiencies of Fukunaga '290 and Fukunaga *et al.* '650 by way of Ueeda *et al.*, stating that:

Ueeda *et al.* discloses at page 1353 that the compound 2-ethoxyadenosine has binding constants at adenosine receptors that vary very little from the binding constants for adenosine, for R-PIA and for NECA, a teaching supporting the conclusion that substitution of an adenosine analog for adenosine would be expected to produce a similar effect, including the analgesic effect on pain.

However, as explained in Applicant's previous response (filed November 19, 2007), Ueeda *et al.* states that 2-ethoxyadenosine is selective for the  $A_{2A}$  receptor, whereas adenosine and NECA are unselective and R-PIA is selective for the  $A_{1A}$  receptor (Ueeda, *et al.*, page 1354, lines 3-4).

Moreover, there are substantial differences in binding constants at  $A_{1A}$  and  $A_{2A}$  receptors between 2-ethoxyadenosine and R-PIA and NECA, while no binding constants whatsoever are given for adenosine. The following table reproduces "-log inhibition constant,  $K_i$  (M)" entries from Table I at page 1353 of Ueeda *et al.* for adenosine, R-PIA, NECA, and 2-ethoxyadenosine. No binding constants are shown for adenosine "because adenosine deaminase is added to the assay medium to destroy endogenous adenosine" (Ueeda, *et al.*, p. 1353, Table I & fn a). By way of illustration, the "-log inhibition constant,  $K_i$  (M)" values are recalculated at the right as "inhibition constant,  $K_i$  (nM)", according to the formula  $K_i$  (nM) =  $10^9 * 10^{(\log \text{ inhibition constant, } K_i \text{ (M)})}$ .

No.		-log inhibition constant, $K_i$ (M)				inhibition constant, $K_i$ (nM)			
		Binding of [ $^3$ H]R-PIA to cortex A <sub>1</sub> AR		Binding of [ $^3$ H]NECA to striatum A <sub>2</sub> AR		Binding of [ $^3$ H]R-PIA to cortex A <sub>1</sub> AR		Binding of [ $^3$ H]NECA to striatum A <sub>2</sub> AR	
		Rat	Guinea pig	Rat	Guinea pig	Rat	Guinea pig	Rat	Guinea pig
1	adenosine (Ado)	-	-	-	-	-	-	-	-
2	NECA	8.11	8.20	8.01	7.72	7.8	6.3	9.8	19
5	R-PIA	8.92	8.44	6.66	7.28	1.2	3.6	219	52
13	2-ethoxyAdo	5.89	5.80	5.82	5.17	1288	1585	1514	6761

As can be seen at the right of the above table, the data from Table I of Ueeda *et al.* corresponds to inhibition constants  $K_i$  in the **nanomolar** range for R-PIA and NECA in rat and guinea pig cortex A<sub>1</sub>A. By contrast, 2-ethoxyadenosine is in the **micromolar** range, and thus is a substantially weaker inhibitor of rat and guinea pig cortex A<sub>1</sub>A by up to **3 orders of magnitude**. Similarly, 2-ethoxyadenosine is a substantially weaker inhibitor of rat and guinea pig striatum A<sub>2</sub>A as compared to R-PIA and NECA. Consequently, the specific data and statements in Ueeda *et al.* directly refute the Examiner's assertion of "binding constants at adenosine receptors that vary very little" between 2-ethoxyadenosine and adenosine, R-PIA and NECA.<sup>2</sup>

#### The Teachings of Ueeda *et al.* Were Known Elsewhere in the Art

The above teachings of Ueeda *et al.* are supported by other references available at the time of the invention, as detailed in the following paragraphs. In view of this art, one of skill would not expect that 2-alkoxyadenosines would be effective at all for the treatment of pain. For example, it was known in the art at the time of invention that A<sub>2</sub>A receptor activation **causes**

<sup>2</sup> The Summary of Ueeda *et al.* states "no marked differences" were observed, but this does not support the Examiner's assertion. Rather, the phrase "no marked differences" refers to similarities, between rat and guinea pig, in the affinities of a given analogue at the A<sub>1</sub>A of brain cortex or at the A<sub>2</sub>A of brain striatum, not similarities between properties of the various analogs.

pain, while A<sub>1</sub>A receptor activation suppresses pain, and further, that selective A<sub>1</sub>A receptor agonists reversed hypersensitivity to pain. Also, A<sub>2</sub>A receptor agonists were known to cause widespread vasodilation and consequent hypotension and tachycardia sufficient to preclude their use as medicaments. Moreover, 2-alkoxyadenosines were known to be very weak A<sub>1</sub>A agonists and weak A<sub>2</sub>A agonists, including spongosine (2-methoxy adenosine). Consequently, one skilled in the art would not expect efficacy in treating pain from weak agonists for A<sub>1</sub>A receptors such as 2-alkoxyadenosines. Further, one skilled in the art would expect that high doses of 2-alkoxyadenosines would be needed to treat pain via A<sub>1</sub>A receptors, and would expect that such doses would also lead to the undesirable side effects of A<sub>2</sub>A receptors, including peripheral pain, hypotension, and tachycardia. One skilled in the art would be motivated instead to pursue selective, high affinity A<sub>1</sub>A receptor agonists for the treatment of pain.

*A<sub>2</sub>A receptor activation causes pain, while A<sub>1</sub>A receptor activation suppresses pain*

A review article on adenosine receptor activation and nociception (Sawynok, Eur. J. Pharmacol. 1998, 317, 1-11) discloses:

In the periphery, adenosine A<sub>1</sub> receptor activation produces pain suppression, while **adenosine A<sub>2</sub> and A<sub>3</sub> receptor activation produces pain enhancement**. Within the spinal cord, adenosine A<sub>1</sub> receptor activation produces antinociception; there are some observations suggesting an additional involvement of adenosine A<sub>2</sub> receptors in such actions, but no data on adenosine A<sub>3</sub> involvement. On the basis of these effects, **adenosine A<sub>1</sub> receptors show a significant potential for therapeutic development**. (emphasis added, page 7, column 1, section 5, lines 5 to column 2, line 3)

Consequently, one skilled in the art would expect A<sub>2</sub>A receptor agonists to cause pain, and would instead investigate A<sub>1</sub>A receptor agonists for treating pain.

*Selective A<sub>1</sub>A receptor agonists reversed hypersensitivity to pain*

Collins *et al.* (Br. J. Pharmacol. 2001, 133 (Proceedings supplement), 48P) discloses that a selective adenosine A<sub>1</sub>A receptor agonist reversed hypersensitivity to pain associated with nerve injury in a rat. It is concluded that adenosine A<sub>1</sub>A agonists may show utility in the

treatment of neuropathic pain in man. However, there is no disclosure or suggestion in this document that a weak, unselective adenosine A<sub>2</sub>A receptor agonist could be used as an analgesic.

*Adenosine A<sub>2</sub>A receptor agonists cause widespread vasodilation and consequent hypotension and tachycardia sufficient to preclude their use as medicaments.*

Vasodilation is reported as the major effect of adenosine A<sub>2</sub>A receptor agonists in several papers. Clear demonstration of reduced blood pressure in rats is reported in Nekooieian *et al.*, Eur. J. Pharmacol. 1996, 307, 163-169. A<sub>2</sub>A induced vasodilation is reported in Mathôt *et al.*, Br. J. Pharmacol. 1996 118, 369-377; Keddie *et al.*, Eur. J. Pharmacol. 1996, 301, 107-113; and Webb *et al.*, J. Pharmacol. Exp. Ther. 1993, 267, 287-295. Selective A<sub>2</sub>A adenosine receptor agonists cause hypotension and tachycardia to a degree sufficient to preclude their use as medicaments (Webb *et al.*, J. Pharmacol. Exp. Ther. 1991, 259, 1203-1212; Casati *et al.*, J. Pharmacol. Exp. Ther. 1995, 275, 914-919; and Bonizzoni *et al.*, Hypertension 1995, 25, 564-569). Selective A<sub>2</sub>A adenosine receptor agonists are potent vasodilators that reduce blood pressure and induce marked increments in heart rate and plasma renin activity. Alberti *et al.*, J. Cardiovasc. Pharmacol. 1997, 30, 320-324. Moreover, as noted in the Ueeda *et al.* document cited by the Examiner, A<sub>2</sub>A receptors in the coronary artery mediate the vasodilatory action of adenosine, and 2-ethoxyadenosine, which is selective for the A<sub>2</sub>A receptor, is a coronary vasodilator.

#### *2-Alkoxyadenosines Are Weak A<sub>1</sub>A Agonists*

The potency of a series of 2- alkoxyadenosines as adenosine A<sub>1</sub>A and A<sub>2</sub>A receptor agonists are described in Ueeda *et al.* J. Med. Chem. 1991, 34, 1334-1339 ("Ueeda *et al.* #2"). "The 2-alkoxyadenosines are very weak agonists at the A<sub>1</sub>A receptors mediating AV block" (page 1339, column 1, final sentence of the "Results and Discussion" section). Moreover, "analogues that are weak A<sub>2</sub>A agonists are also unselective, for example, 3a" where 3a is spongosine (2-methoxyadenosine) (left column, last sentence of second paragraph and Table III, entry 3a).

***The Cited Art Does Not Provide Reason or Motivation to Use Alkoxyadenosines***

Because the Fukunaga compounds cited by the Examiner are shown in Ueeda *et al.* to have substantially different binding constants at A<sub>1</sub>A and A<sub>2</sub>A receptors as compared with 2-ethoxyadenosine, and other art at the time of the invention would lead one away from weak A<sub>2</sub>A receptor agonists such as 2-alkoxyadenosines, there is no reason or motivation to use 2-ethoxyadenosine in the methods of the Fukunaga patents. Moreover, a showing of motivation cannot be based on broad conclusory statements lacking evidentiary support. The Examiner's argument contains erroneous or at best conclusory statements about Ueeda *et al.* and therefore fails to address Applicant's detailed arguments and evidence showing the actual teachings of Ueeda *et al.* Because the Examiner's argument presents no **evidence, and does not address Applicant's evidence**, it cannot support a reason or motivation to combine Ueeda *et al.* with the Fukunaga patents to arrive at the claimed method.

***Legal standards for showing of motivation to modify prior art teachings not met***

While the locus of the suggestion or motivation need not be expressly stated in the prior art reference, the Courts have held that a showing of suggestion or motivation in the prior art must nevertheless be supported by evidentiary findings of fact, and that broad conclusory statements do not constitute such evidence of a showing of suggestion or motivation:

Often, it will be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. **To facilitate review, this analysis should be made explicit.** See *In re Kahn*, 441 F. 3d 977, 988 (CA Fed. 2006) (“[R]ejections on obviousness grounds **cannot be sustained by mere conclusory statements**; instead, there must be some **articulated reasoning** with some **rational underpinning** to support the legal conclusion of obviousness”). (Bold emphasis added, *KSR v. Teleflex*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007))

As discussed elsewhere, the Fukunaga patents are deficient in any suggestion or motivation to arrive at the compound of Applicant's claimed method, namely spingosine (2-methoxyadenosine). The Examiner has attempted to cure this deficiency by asserting that:

Ueeda *et al.* discloses at page 1353 that the compound 2-ethoxyadenosine has binding constants at adenosine receptors that vary very little from the binding constants for adenosine, for R-PIA and for NECA, a teaching supporting the conclusion that substitution of an adenosine analog for adenosine would be expected to produce a similar effect, including the analgesic effect on pain.

However, the Examiner's assertions regarding the binding constants in Ueeda *et al.* are erroneous or at best conclusory. The Examiner provides no basis for the conclusion that "2-ethoxyadenosine has binding constants at adenosine receptors that vary very little from the binding constants for adenosine, for R-PIA and for NECA." By contrast, as detailed elsewhere herein, the evidence in Ueeda *et al.* shows substantial differences in the binding constant for 2-ethoxyadenosine at cortex A<sub>1</sub>A and striatum A<sub>2</sub>A in rat and guinea pig as compared to R-PIA and NECA. Moreover, Ueeda *et al.* discloses no binding constant whatsoever for adenosine at cortex A<sub>1</sub>A and striatum A<sub>2</sub>A. Because the Examiner's argument presents no evidence, and does not address Applicant's evidence, it cannot support a reason or motivation to combine Ueeda *et al.* with the Fukunaga patents to arrive at the claimed method.

*Prior art must suggest the specific modification*

Turning to the more specific question of obviousness of a chemical compound in a claimed invention, the motivation or suggestion to modify the prior art teachings must be specific with regard to the chemical modification required. *In re Deuel* 34 USPQ2d 1210 (Fed. Cir. 1995). The Federal Circuit in *Deuel* reaffirmed the requirements for establishing *prima facie* obviousness of chemical compounds. The Court explained that while known compounds may suggest some categorically similar compounds (e.g., homologs, isomers), the question of obviousness turned on whether the prior art would have suggested the "specific molecular modification" necessary to arrive at the claimed compound:

Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs ... Similarly, a known compound may suggest its analogs or isomers, either geometric isomers (cis v. trans) or position isomers (e.g., ortho v. para).

In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention. See *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992); *In re Dillon*, 191 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc) ('structural similarity between claimed and prior art subject matter, ... where prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness'), ... *In re Grabiak*, 769 F.2d 729, 731-2, 226 USPQ 870, 872 (Fed. Cir. 1985) ('[I]n the case before us there must be adequate support in the prior art for the [prior art] ester/[claimed] thioester change in structure, in order to complete the PTO's prima facie case and shift the burden of going forward to the applicant.') *In re Lahu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ('The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.') *Deuel* at 1214, 1215 (underline emphasis added, italics in original).

Thus, a *prima facie* case of obviousness is established for a chemical composition where there is structural similarity between the claimed and reference compounds and where the prior art gives reason or motivation to make the claimed compounds. With regard to the motivation prong of the *prima facie* case, the prior art must suggest the specific molecular modification—not modification generally-- needed to arrive at the compounds used in the claimed invention.

The Examiner cites no teaching or suggestion in either Fukunaga '290 or Fukunaga *et al.* '650 to make any other specific structural modifications to the compounds described therein, let alone to arrive at alkoxy substituted adenosines or 2-alkoxy substituted adenosines. Further, the recitation in the Fukunaga patents of broad, generic terms such as "adenosine compound," "adenine nucleotides," "derivatives and analogs of adenosine," or the like are but broad generalizations that certainly do not in any way identify the specific molecular modification needed to arrive at the compound in Applicant's claimed invention. Also, as described elsewhere herein, Ueeda *et al.* does not motivate one of skill in the art to contemplate the use of 2-ethoxyadenosine in the methods of the Fukunaga patents because of the stark differences in properties between 2-ethoxyadenosine and the specific compounds of the Fukunaga patents.

In any event, mere conclusory statements about what is present in the prior art, without supporting evidence, do not constitute evidence for showing motivation or suggestion to modify the teachings of the prior art. The Examiner's showing of motivation to modify the cited

references to arrive at Applicants' claimed compounds therefore does not meet the legal standards set forth in the relevant case law. The Examiner's argument is incorrect because reliance on mere conclusory statements does not meet the Office's obligation provide particular findings of fact.

***The Homology Analysis is Not Relevant to the Claimed Invention in View of the Cited Art***

In this rejection, the Examiner relies on "The Homology Rule," citing *In re Hass et al.* (CCPA 1944) 141 F2d 122, 127, 60 USPQ 544, 548, *In re Henze* (CCPA 1950) 181 F2d 196, 85 USPQ 261, and M.P.E.P. §2144.09. The Examiner asserts that "[i]n light of the Hass/Henze doctrine the instant claims are deemed to have been rendered obvious by the disclosure of the noted Ueeda *et al.* reference in view of the disclosures of the Fukunaga references." Further, the Examiner characterizes Applicant's previous arguments (*i.e.*, set forth in the Reply filed on November 19, 2007) concerning this rejection as follows:

The point of examiner's rejection was to note that a compound exists and is known in the prior art (2-ethoxyadenosine disclosed by Ueeda *et al.*) that would be expected, based on the disclosures of the Fukunaga patents and Ueeda *et al.* to have pharmacological properties very similar to the compound (spongosine, aka 2-methoxyadenosine) applicant's claims and disclosure identify as an active analgesic.

The Examiner thus alleges homology between 2-ethoxyadenosine of Ueeda *et al.* and spongosine (2-methoxyadenosine) of the claimed invention.

However, because Ueeda *et al.* provides no reason or motivation to use 2-ethoxyadenosine in the methods of the Fukunaga patents, the Examiner's focus on homology between 2-ethoxyadenosine and spongosine (2-methoxyadenosine) is not relevant. Since the compounds cited by the Examiner from the Fukunaga patents are shown in Ueeda *et al.* to have substantially different binding constants at A<sub>1</sub>A and A<sub>2</sub>A receptors as compared with 2-ethoxyadenosine, Ueeda *et al.* provides no reason or motivation to use any alkoxyadenosine at all in the methods of the Fukunaga patents, let alone 2-ethoxyadenosine, or the spongosine (2-methoxyadenosine) of the claimed invention.

### **Conclusion**

Consequently, for at least the above reasons, a *prima facie* case of obviousness has not been made and the claimed methods are patentable over Fukunaga '290 in view of Fukunaga *et al.* '650, and further in view of Ueeda *et al.* Applicant respectfully requests that the corresponding rejections be withdrawn.

### **Rejections under 35 U.S.C. § 112, 1<sup>st</sup> Paragraph re Written Description**

Claims 11, 15, 18, and 32-46 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner alleges that there is inadequate written description regarding: the "prevention" of pain associated with any disease condition by the administration of the 2-methoxyadenosine; the coadministration of 2-methoxyadenosine with any other substance known to act as an analgesic; or, the effective treatment of pain associated with the recited diseases.

### ***Regarding "Prevention"***

Applicant respectfully maintains that the rejections alleging insufficient written description of the "prevention" of pain are improper or incorrect, for at least the reasons explained in detail in the response to the preceding Office Action. Nevertheless, because Applicant has canceled claims 15, 18, and 32-46, the corresponding rejections are moot, and Applicant respectfully request that they be withdrawn. Further, since claim 11 does not recite the term "prevention," the rejection should be withdrawn insofar as it relates to claim 11.

Applicant wishes to point out that new claims 47-52 find explicit support in the specification, for instance, in working, *in vivo* Example 1, which employs a carrageenan induced thermal hyperalgesia (CITH) model in the rat. (specification, page 7, line 23 to page 8, line 2). As an inflammatory stimulus, "[c]arrageenan (2%, 10 microlitres) was administered into the right hind paw," and "[s]pongine was administered at the same time as carrageenan." Consequently, support is provided for claim 47, "wherein the spongine is administered to the subject when the subject is at risk of developing inflammation," and also claim 48, "wherein the

spongosome is administered to the subject when the subject is contacted with an inflammatory stimulus.” The carageenan and the spongosome are administered before “[a] heat source was placed close to the treated and untreated hind paws” as a pain stimulus” (**before** because the heat source was placed close to the **treated** paw). Consequently, Example 1 provides written description for claim 49, “wherein the spongosome is administered to the subject when the subject is at risk of developing pain,” and likewise claim 50, “wherein the spongosome is administered to the subject before the subject is exposed to a pain stimulus.” Similarly, support is provided for claim 51, “wherein the pain is associated with or caused by inflammation,” and claim 52, “wherein the pain is associated with or caused by thermal hyperalgesia.” Further, as the Examiner acknowledges, “pain being treated, [is] a possibility clearly addressed by, and enabled by, the supplied examples” (Office Action, page 3, lines 4-5).

*Regarding “Co-administration”*

The Examiner maintains the allegation that “there is no written description supporting adequately the coadministration of 2-methoxyadenosine with any other substance known to act as an analgesic.” However, as Applicant explained in the response to the preceding action, the rejection should be withdrawn because the specification includes written description showing the observed, additive anti-hyperalgesic effect of 2-methoxyadenosine when co-administered with the analgesic gabapentin. For example, claim 27 recites “further comprising administering an analgesic agent other than spongosome to the subject.” **Gabapentin is an analgesic** other than spongosome as described in the specification, *e.g.*, “other analgesic agents that may be administered with spongosome include ...gabapentin” (page 6, lines 19 and 24). **Gabapentin and spongosome are coadministered** *e.g.*, as shown in FIG. 5 and Example 5. For example, FIG. 5 shows “the **additive** effect of spongosome and gabapentin in a model of neuropathic pain.” (page 7, lines 19-20). Example 5 states that “Spongosome and gabapentin were administered (p.o.) in different **proportions** as indicated in” FIG. 5 to result in the “**total dose** administered [as] shown on the horizontal axis.” (page 9, lines 2-4). Since the spongosome and gabapentin are administered in different proportions to make up a total dose, leading to an “observed effect” comparable to a theoretical “additive effect,” Example 5 supports co-administration, *e.g.*, “further comprising administering an analgesic agent other than spongosome to the subject,” as

recited in claim 27. Moreover, as the Examiner acknowledges, "pain being treated, [is] a possibility clearly addressed by, and enabled by, the supplied examples" (Office Action, page 3, lines 4-5). Therefore, the allegation that "there is no written description supporting adequately the coadministration of 2-methoxyadenosine with any other substance known to act as an analgesic" is incorrect. Applicant respectfully requests that the rejection be withdrawn.

*Regarding "Diseases"*

Applicant respectfully maintains that the rejections alleging insufficient written description of treatment of pain associated with the recited diseases are improper or incorrect for at least the reasons explained in detail in the response to the preceding Office Action. Nevertheless, because Applicant has canceled claims 15, 18, and 32-46, the corresponding rejections are moot, and Applicant respectfully request that they be withdrawn. Further, since claim 11 does not recite the diseases that are the object of the Examiner's rejection, the rejection should be withdrawn insofar as it relates to claim 11. Applicant wishes to point out that as the Examiner acknowledges, "pain being treated, [is] a possibility clearly addressed by, and enabled by, the supplied examples" (Office Action, page 3, lines 4-5), *e.g.*, *in vivo* pain examples that model pain conditions including inflammation (Example 1), hyperalgesia (Examples 1 and 2), damaged neurons (Example 2), and neuropathy or allodynia (*e.g.*, Examples 4 and 5).

For at least the preceding reasons, the rejections of claims 11, 15, 18, and 32-46 under 35 U.S.C. §112, first paragraph, regarding written description are moot or overcome. Applicant respectfully requests that the corresponding rejections be withdrawn.

**Rejections under 35 U.S.C. § 112, 1<sup>st</sup> Paragraph re Enablement**

Claims 11-31 stand rejected under 35 U.S.C. §112, first paragraph, because while the Examiner acknowledges that the specification is enabled for the treatment of inflammation and hypertension, the Examiner alleges that the specification does not reasonably provide enablement for the treatment of any other disease condition.

Applicant respectfully maintains that the rejections alleging lack of enablement for the treatment of any other disease condition are improper or incorrect, for at least the reasons

explained in detail in the response to the preceding Office Action. Nevertheless, because Applicant has canceled claims 15 and 18, the corresponding rejections are moot, and Applicant respectfully request that they be withdrawn. Further, since none of the remaining claims recite the diseases that are the object of the Examiner's rejection, the corresponding rejections should also be withdrawn. Applicant wishes to point out that as the Examiner acknowledges, "pain being treated, [is] a possibility clearly addressed by, and enabled by, the supplied examples" (Office Action, page 3, lines 4-5), *e.g.*, *in vivo* pain examples that model pain conditions including inflammation (Example 1), hyperalgesia (Examples 1 and 2), damaged neurons (Example 2), and neuropathy or allodynia (*e.g.*, Examples 4 and 5). Consequently, the full scope of the claims, *e.g.*, "[a] method of treating pain which comprises administering spongiosine (2-methoxyadenosine) to a subject in need of such treatment" as recited in claim 11, is enabled.

**Rejection of Claims 14, 18, 27 and 44 under 35 U.S.C. § 112, 2<sup>nd</sup> Paragraph**

Claims 14, 18, 27 and 44 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Regarding claim 14, the Examiner alleges that the term "disease that causes damage to sensory neurons" renders the claim incomplete because the particular diseases have not been defined in the claim. Applicant respectfully maintains that the rejection is improper since the plain meaning of the generic term "disease that causes damage to sensory neurons" is clear to one of ordinary skill in the art in the context of the specification, as discussed in detail in Applicant's previous response (filed November 19, 2007). Nevertheless, Applicant has amended claim 14 to recite "wherein the pain is caused by or associated with damaged sensory neurons," as supported throughout the specification, *e.g.*, the treatment of hyperalgesia caused by or associated with damaged sensory neurons in the chronic constriction injury model of neuropathic pain as shown in FIG. 2 and Example 2. Since the "pain" treated in claim 14 is defined in the claim as "caused by or associated with damaged sensory neurons," the corresponding rejection of claim 14 is overcome.

Regarding claim 27, the Examiner maintains the allegation that a term such as "further comprising" is missing. Applicant respectfully maintains that the rejection is improper since the new term "an analgesic agent" maintains proper antecedent basis with claim 11, as discussed in

detail in Applicant's previous response (filed November 19, 2007). Nevertheless, Applicant has amended claim 27 herein to recite "further comprising," according to the Examiner's suggestion. Applicant notes that claim 11, which recites in part "administering spongiosine (2-methoxyadenosine) to a subject in need of such treatment" is generic for any such subject in need of treatment, for example, a subject to which "an analgesic agent other than spongiosine" has already been administered.

The Examiner suggests that clarity would be improved by amendment of the term "an analgesic agent," since the Examiner considers that spongiosine is in effect a "first" analgesic agent. Applicant respectfully submits that amendment of claim 27 to recite "an analgesic agent other than spongiosine" should address the issue of clarity.

Because claims 18 and 44 are canceled, the rejection thereof is moot.

Applicant respectfully submits that for at least the preceding reasons, the rejections of claims 14, 18, 27 and 44 under 35 U.S.C. § 112, 2nd paragraph are moot or overcome, and should therefore be withdrawn.

#### **Obviousness-type double patenting rejections**

Claims 11-46 stand provisionally rejected under the judicially created doctrine of obviousness type double patenting over claims 16-33 of co-pending Application Ser. No. 10/547,455, filed March 5, 2004, and claims 13-24 of co-pending Application Ser. No. 10/547,454, filed March 5, 2004.

The allegedly conflicting claims of Application Ser. Nos. 10/547,455 and 10/547,454, have not been patented. For this reason, the present rejection is a provisional obviousness-type double patenting rejection. Applicant will address any obviousness type patenting rejections upon notification that there are claims which are otherwise allowable.

#### **CONCLUSION**

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (650) 839-5078.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050.

Respectfully submitted,

Date:

Aug 7, 2008



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